Cell Host & Microbe
Editorial

Microbes "R" Us

It has long been recognized that microbes of all kinds abound—living around us, on us, within us, and even being a part of our DNA. Understandably, however, most research has focused on microbes that cause obvious disease. Also, endogenous microbes were seldom considered as an influencing factor when investigating disease mechanisms. All this has been rapidly changing, and a newfound interest in and a respect for the multitude of endogenous microbes that inhabit our bodies and influence us in various ways have been emerging. This, the fourth annual review issue of *Cell Host & Microbe*, was conceived to capture some vignettes and excitement from the emerging understanding of endogenous microbes and the roles they play in host health and disease. As illustrated on the cover and in the Reviews and Minireviews in this issue, endogenous microbes constitute a pivotal hub that regulates various aspects of host physiology.

Our bodies host trillions of microbial cells representing millions of unique microbial genes, which work in addition to and in conjunction with our genes to regulate human physiology. Recognizing this, in 2007, the NIH funded the 5 year Human Microbiome Project (HMP) that was "specifically devised and implemented to create a set of data, reagents, or other material whose primary utility will be as a resource for the broad scientific community." This project is just coming to culmination, and in a Commentary, Lita Proctor (pp. 287–291) provides an update on where things stand with the HMP and looks forward to the challenges and opportunities ahead. The data arising from the HMP and other sources raise the tantalizing possibility of using human-associated microbial signatures as predictive tools in clinical and forensic settings. However, as discussed by Rob Knight and colleagues (pp. 292–296), given the inter- and intraindividual variability of the microbiome, significant challenges exist before we can consider microbiome data for diagnostic applications. Knight and colleagues examine the predictive value of host-associated microbial signatures, discuss the challenges involved, and suggest solutions for filtering through the high variability associated with such data.

Perhaps the best recognized role of the microbiota is in regulating the host's immune system, particularly in the gut, and this has obvious ramifications for a multitude of diseases both local and distal. Dan Littman and Eric Pamer (pp. 311–323) review the role of the microbiota in regulating immune development and function. They also discuss the factors, such as antibiotics, that alter homeostasis between the microbiota and host immunity to induce dysbiosis and its disease causing consequences. The distal effects of the microbiota on immunity are discussed by Diane Mathis and Christophe Benoist (pp. 297–301) in the context of autoimmunity, which leads them to reexamine the concepts of "self" and "nonself." Altered homeostasis is a well-defined path to malignancy. Claudia Plottel and Martin Blaser (pp. 324–335) examine the influence of endogenous microbes on mechanisms that cause cancer. To illustrate how the metabolism of endogenous microbes could influence cellular homeostasis, they present the concept of the estrobolome, wherein they consider the gene products of endogenous enteric microbiota that are capable of metabolizing estrogens, and regulating systemic estrogen obviously affects gender-specific malignancies. The microbiota in the gut, which represents multiple species, is a veritable metabolic factory. Justin Sonnenburg and Michael Fischbach (pp. 336–347) discuss metabolism as a critical consideration of how different bacterial species within a host-associated community interact. The authors' discussions clearly illustrate that one bacterium's waste is another's means to acquiring energy, which helps maintain the stability of host-associated microbial communities. As any child instructed to regularly brush their teeth will tell you, our mouths are also home to vast microbial communities. Richard Darveau, Michael Curtis, and colleagues (pp. 302–306) give us a bird's eye view of our current understanding of the diversity of the oral microbiome. The authors explain how our mouths normally tolerate such a high bacterial load and how disruptions in host homeostasis or the oral microbiota can lead to periodontal disease.

Although a lot of the microbiome-focused research has been directed towards vertebrates, invertebrates and plants harbor endogenous microbes—and understanding those systems can be very instructive. As Angela Douglas (pp. 359–367) illustrates in her Review, insects host a number of microbes that they depend on for nutrition, defense, and general well being. Considering the more defined composition of the insect microbiota, as the author points out, insects may in fact represent an ideal model system to study the principles of host-microbiota interactions. Insects also serve as vectors for human pathogens. As discussed by George Dimopoulos and colleagues (pp. 307–310), the insect microbiota is now recognized to influence vector competence, and manipulating vector microbiota could represent a means of controlling disease transmission, giving further impetus for studying insect-associated endogenous microbes. Higher plants also display a remarkable ability to form symbiotic associations with microbes, often relying on their microbial partners for nutrient uptake. In turn, the microbe gets privileged access to carbon sources. Exemplary of this is the legume-rhizobial symbiosis, which causes significant developmental and metabolic changes for both the microorganism and host, while providing the plant with much-needed fixed nitrogen. New organs called nodules develop on the roots of plants to host the microbes. Guilhem Desbrosses and Jens Stougaard (pp. 348–358) discuss nodulation by rhizobia as an example of how microorganisms and plants have coevolved and how microbial colonization affects plant developmental pathways.

What about viruses? As pointed out in the Proctor Commentary, the microbiome also constitutes endogenous viruses, the virome. As the Plottel and Blaser Review illustrates, any latent virus is part of the host's virome and can thus be considered an endogenous virus. But perhaps the most telling in this regard are endogenous viral elements (EVE) within our genomes, footprints left by not only

retroviruses—which are known to integrate into the host genome—but also by RNA viruses with no DNA intermediate and single-stranded DNA viruses. Edward Holmes (pp. 368–377) discusses these EVEs, exploring how these viral remnants were left behind and what they tell us about the evolutionary arms race between hosts and viruses.

With all the knowledge gained about endogenous microbes within various hosts, it would seem that higher organisms are just borrowing time and space in a microbial world. Knowing that there are more microbes in our body than cells elicits a sense of awe for these tiny beings, our endogenous partners. While your specific research interests might be centered on a particular pathogen, specific pathogenic mechanisms, or aspects of the immune system, we hope you will read the reviews in this issue and start to consider the interactions of your favorite pathogen with the host—or the specific immune mechanism in the complex context of the endogenous microbes that the host already harbors.

A note of sincere thanks to our authors and reviewers, whose efforts are clearly visible in these informative, insightful, and thought-provoking Reviews, Minireviews, and Commentaries. We hope you enjoy reading this issue as much as we enjoyed putting it together. We look forward to your feedback, so please email us at hostmicrobe@cell.com.

DOI 10.1016/j.chom.2011.10.005